Lactic Acidosis as Presenting Symptom of Thiamine Deficiency in Children with Hematologic Malignancy

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Abstract

Thiamine is an essential component of cellular metabolism and its deficiency results in potentially life-threatening events and profound lactic acidosis through anaerobic metabolism. Acute decompensation in thiamine-deficient patients may manifest as neurologic or cardiovascular changes, with severe lactic acidosis as the presenting symptom. We describe two hematological pediatric patients with thiamine deficiency and hemodynamic instability who improved following thiamine supplements. Thiamine levels were inversely proportional to lactic acidosis; specifically, lower thiamine levels were related to higher lactate levels. We recommend that children with hematological malignancies admitted to a pediatric intensive care unit with low blood pressure and lactic acidosis should be considered for thiamine-level screening and receive supplementation accordingly.

Keywords
- thiamine deficiency
- lactic acidosis
- hematologic malignancy

Introduction

Acute decompensation of patients with hematological malignancies may be a result of metabolic impairment due to the tumor per se, posthematopoietic cell transplantation, an infectious process (sepsis), or cerebrovascular insult. The decompensation may also be a result of thiamine deficiency and manifest as neurologic changes, such as neuropathy and encephalopathy, or it may be metabolic and manifest as severe lactic acidosis.[1–3]

Lactic acidosis is a potentially life-threatening event that may occur in primary and acquired diseases. Primary lactic acidosis includes inherited disorders of energy metabolism. Acquired lactic acidosis in patients with malignancy may be due to hypoperfusion, liver or renal failure, diabetes, infections, sepsis, major surgery, metabolic complication of malignancies, and thiamine deficiency. Lactic acidosis may also result from metabolic impairment due to the tumor itself, from inadequate support of thiamine with total parenteral nutrition (TPN), or from a combination of the two.[1]

Thiamine is an essential water-soluble B vitamin absorbed in the small intestine. It is vital as a coenzyme for carbohydrate and amino acid metabolism. In its biologically active form, thiamine pyrophosphate, it is a key cofactor for pyruvate dehydrogenase and 2-oxoglutarate (α-ketoglutarate) dehydrogenase. Since both enzymes are required for the generation of adenosine triphosphate through anaerobic glycolysis, thiamine deficiency may result in metabolic crisis leading to lactic acidosis and death.[2] Inadequate stores of thiamine result in the failure of pyruvate to enter the tricarboxylic acid cycle. This may prevent aerobic metabolism, which may lead to profound lactic acidosis through anaerobic metabolism.[3]

In this report, we describe two pediatric hematological patients with thiamine deficiency who presented with

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Table 1 Laboratory values of patient 1

Variable	At admission	At discharge
White blood count (K/μL)	990	1,810
Hemoglobin (g/dL)	8.9	10.2
Platelets (K/μL)	17,000	5,000
Sodium (mEq/L)	144	142
Potassium (mEq/L)	2.9	3.3
Bicarbonate (mEq/L)	15.1	30.8
Blood urea nitrogen (mg/dL)	42	87
Serum creatinine (mg/dL)	0.52	0.54
Lactate (mg/dL)	79	16

hemodynamic instability and hyperlactatemia, which improved following thiamine supplements. The intent of this report is to raise the level of awareness of this preventable complication.

Case Report

Case 1

A 4-year-old boy diagnosed with juvenile myelomonocytic leukemia s/p bone marrow transplantation 35 days prior to admission was admitted to the pediatric intensive care unit (PICU) due to protracted diarrhea, electrolyte disturbances, and hyperlactatemia. His temperature was 36.9°C, blood pressure 101/64 mm Hg, pulse 123 beats/minute, respiratory rate 13 breaths per minute, and oxygen saturation 100% on room air. He had no neurologic impairment, his heart rate was regular with no murmurs, and his breath sounds were normal. His abdomen was distended with diffuse tenderness and hepatomegaly. The lactate level was 100 mg/dL. Additional laboratory data are listed in ►**Table 1**. His chest X-ray and echocardiogram were unremarkable.

Thiamine levels were measured as thiamine pyrophosphate percentage response to erythrocyte transketolase activity. We used the B1 Chrome System HPLC Assay Kit (Eagle Biosciences, Nashua, New Hampshire, United States), which makes a quantitative determination of thiamine pyrophosphate levels. The normal range is 0 to 15%, the range for a medium risk for thiamine deficiency is 15 to 20%, and the range for a high risk for thiamine deficiency is 20% and above. The patient above had a medium risk (15.2%) thiamine pyrophosphate effect.

While in the PICU, his blood pressure dropped and he required inotropic support for a few hours in addition to fluid resuscitation. Shortly after receiving thiamine supplements (IV 10 mg once daily) due to low thiamine levels, his blood pressure stabilized, the adrenaline drip was stopped, and his lactate levels went down to normal range (►**Fig. 1**). He was discharged to the hematology–oncology unit for further treatment.

Case 2

A 10-year-old boy was admitted to the PICU due to suspected Burkitt's lymphoma. His temperature was 37.6°C, blood pressure 80/40 mm Hg, pulse 99 beats/minute, respiratory rate 43 breaths per minute, and oxygen saturation 92% on room air. The heart rate was regular with no murmurs. The physical examination revealed lethargy, convulsions, dyspnea and tachypnea, and the patient required pleurocentesis and oxygen support for pleural effusion. The abdomen was distended with diffuse tenderness and it had a laparotomy scar due to a splenectomy (thalassemia major). The lactate level upon admission was 75 mg/dL and it later rose to 153 mg/dL. The thiamine level was low (56.6 nmol; normal

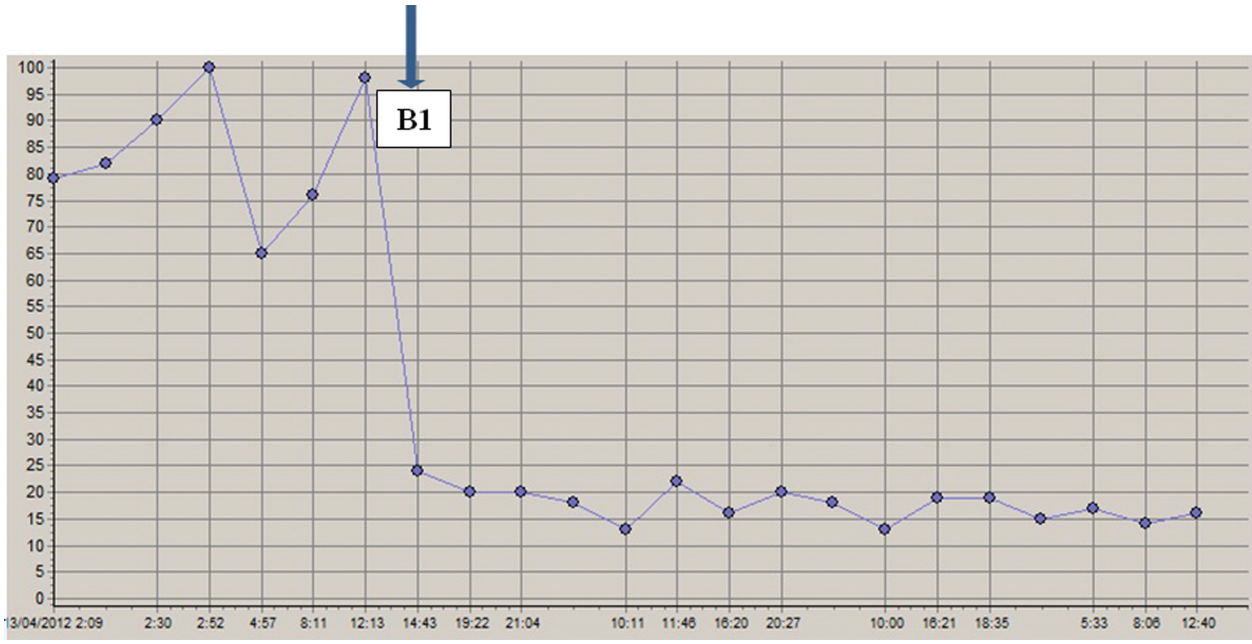

Fig. 1 Lactate levels of patient 1 during hospitalization. B1 = administration of thiamine supplements.

Table 2 Laboratory values of patient 2

Variable	At admission	At discharge
White blood count (K/μL)	11,170	10,730
Hemoglobin (g/dL)	10.6	7.8
Platelets (K/μL)	509,000	309,000
Sodium (mEq/L)	132	134
Potassium (mEq/L)	4.4	3.9
Bicarbonate (mEq/L)	14	29.3
Blood urea nitrogen (mg/dL)	75	23
Serum creatinine (mg/dL)	0.53	0.47
Lactate (mg/dL)	75	27

range: 66.5–200 nmol/L, tested by the high-performance liquid chromatography HPLC fluorescence detector). Other laboratory data are listed in ►**Table 2**. Chest X-ray revealed a small, residual pleural effusion. The echocardiogram was unremarkable. His brain computed tomography revealed suspected retrobulbar infiltration, most probably in correlation with posterior reversible encephalopathy syndrome.

The low blood pressure was treated by continuous inotropic support with dopamine. He received wide-spectrum antibiotics and bicarbonate due to his general poor status and lactic acidosis. The patient was also treated with thiamine supplements (intravenous, IV, 10 mg once daily) due to low thiamine levels. Following thiamine treatment, his blood pressure stabilized, the dopamine drip was stopped, and his lactate levels went down to normal range (►**Fig. 2**). His neurologic status also improved and he was transferred to the hematology–oncology unit for further treatment.

Discussion

Lack of thiamine can lead to potentially life-threatening events. Inadequate stores of thiamine result in the failure of pyruvate to enter the tricarboxylic acid cycle, thus preventing aerobic metabolism, which may lead to profound lactic acidosis through anaerobic metabolism.[3] Deficiencies in thiamine may also lead to an array of clinical sequelae, including peripheral and central neuropathies (dry beriberi), cardiovascular disease (wet beriberi), metabolic coma, Wernicke encephalopathy, Korsakoff syndrome, and optic neuropathy.[2] Wernicke–Korsakoff (WK) syndrome was historically most commonly associated with alcohol abuse among adults. However, a variety of mechanisms might predispose to thiamine deficiency, which alone can cause the full spectrum of the characteristic clinical signs (nonalcoholic WK syndrome [non-alcWKS]). In a recent study that systematically reviewed more than 125 years of case reports of non-alcWKS, it was shown that the similarities in clinical manifestations of acute and chronic WK were striking. A wide variety of precipitating illnesses led to non-alcWKS. Multiple risk factors for thiamine deficiency were also evident within individual cases, such as prolonged parenteral feeding.[4,5] It is important to keep in mind that early detection and prompt treatment of thiamine deficiency may prevent acute neuronal death and may prevent the disease from progressing to chronic disability.[5]

Thiamine deficiency has also been seen in other conditions associated with malnourishment, such as bariatric surgery, malignancy, hyperemesis gravidarum, Crohn disease, starvation, immunodeficiency syndrome, malabsorption, dialysis, diuretics, hyperthyroidism, sepsis, and increased metabolic demand. Primary thiamine deficiency is caused by genetic factors and defective transport. Thiamine deficiency may appear due to prolonged IV dextrose solutions/TPN with inadequate support of thiamine or among children whose

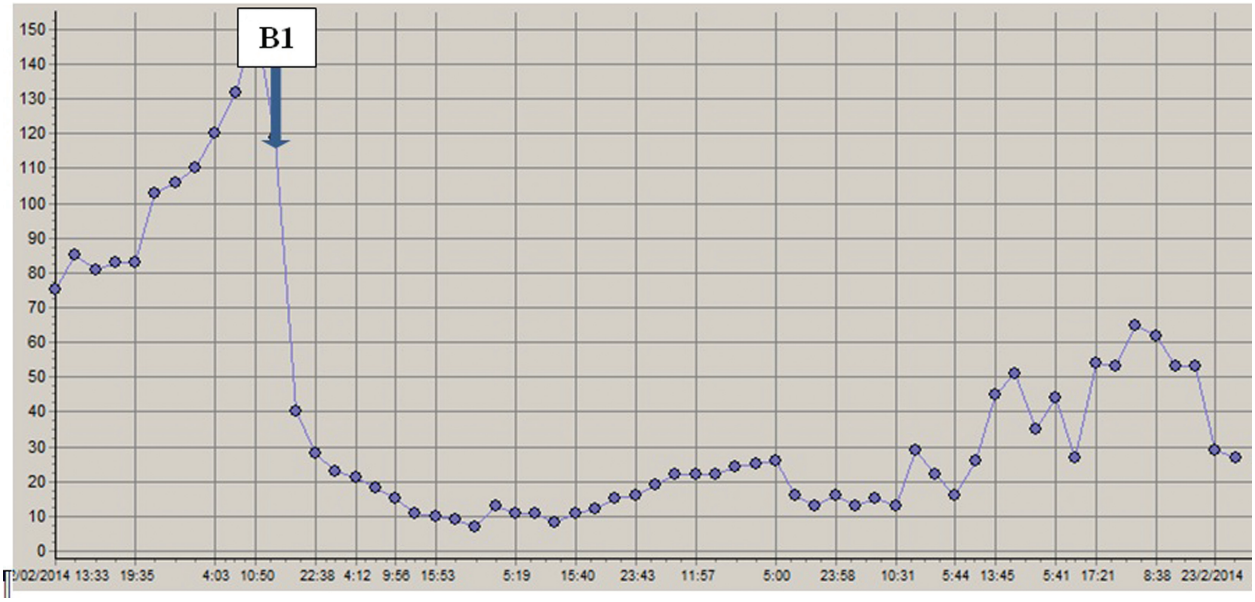

Fig. 2 Lactate levels of patient 2 during hospitalization. B1 = administration of thiamine supplements.

diets were identified as being deficient in thiamine. The presence of graft versus host disease of the intestines may also cause thiamine deficiency through malabsorption and vomiting.[1,6]

In hematological malignancies, methotrexate may compete with the thiamine transport systems by reducing the availability of thiamine, which may cause lactic acidosis by the same mechanism as that described in case of thiamine deficiency.[7] The sudden onset of the symptoms and the short interval between thiamine drop-off and the clinical manifestations are explained by the lack of a storage mechanism for thiamine, which renders its supply dependent upon regular daily intake via nutrition.[1]

There is a paucity of information on thiamine deficiency in the pediatric population.[8] Thiamine deficiency has been reported in diverse populations and patient groups and may be clinical or subclinical (more common among the critically ill), with a prevalence of 20% at admission to the ICU and 21% on admission to emergency departments. It was observed in 7.5% of a group of schoolchildren and more than 10% of that group presented with borderline thiamine status.[9–11] Seear et al examined the incidence of thiamine deficiency in three high-risk pediatric populations and measured the vitamin levels of 80 children admitted to a PICU for more than 2 weeks. They found that 12.5% of 80 patients receiving intensive care and 4 of 6 patients receiving chemotherapy were thiamine deficient.[12] Thiamine levels may further deplete over time in different groups of ICU patients, such as those with acute renal failure requiring continuous renal replacement therapies or those undergoing cardiac surgery.[9,10] Thiamine is also important in the synthesis of the antioxidants nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, and glutathione, which mitigate the oxidative stress that accompanies septic shock.[2] In addition, thiamine deficiency through insufficient adenosine triphosphate generation combined with toxic effects of reactive oxygen species can lead to acute tubular necrosis through ischemia-reperfusion injury and electrolyte imbalance.[13]

In a prospective Brazilian study, Lima et al evaluated the incidence of thiamine deficiency in 202 critically ill children upon admission to the PICU and determined the risk factors associated with this deficiency.[10] The most relevant findings of their study were that low blood thiamine levels were highly prevalent upon admission to the PICU (28.2%) and that thiamine deficiency was associated with higher mortality among patients with severe sepsis/septic shock.

The thiamine levels of our presented cases were lowered in the presence of lactic acidosis and normalized once thiamine supplements were introduced. This finding may indicate a correlation between the deficiency of thiamine and increased metabolic demands, since both patients who had hemodynamic instability also had higher lactate levels.

Conclusion

In conclusion, lack of thiamine may be prevalent in critically ill hematologic patients. We suggest that a child that is admitted to the PICU with hemodynamic instability and acidosis should be empirically treated with thiamine, given that any delay in treatment can lead to irreversible damage. This recommendation is further supported by the evidence that emerged in a review of the literature. Because there are few successful therapeutic interventions available for these patients, repletion of B1 vitamins (thiamine) might be an easy and safe way to help reverse lactic acidosis in hematological patients. Although there are many case reports on this subject, larger qualitative studies are lacking and additional studies with larger samples should be performed to validate these results. In addition, given the high frequency of residual morbidity, studies should focus on decreasing diagnostic and treatment delay.

References

1 Svahn J, Schiaffino MC, Caruso U, Calvillo M, Minniti G, Dufour C. Severe lactic acidosis due to thiamine deficiency in a patient with B-cell leukemia/lymphoma on total parenteral nutrition during high-dose methotrexate therapy. J Pediatr Hematol Oncol 2003; 25(12):965–968

2 Da Silva YS, Horvat CM, Dezfulian C. Thiamine deficiency as a cause of persistent hyperlactatemia in a parenteral nutrition-dependent patient. JPEN J Parenter Enteral Nutr 2015;39(5): 604–606

3 Donnino MW, Carney E, Cocchi MN, et al. Thiamine deficiency in critically ill patients with sepsis. J Crit Care 2010;25(4): 576–581

4 Isenberg-Grzeda E, Alici Y, Hatzoglou V, Nelson C, Breitbart W. Nonalcoholic thiamine-related encephalopathy (Wernicke-Korsakoff syndrome) among inpatients with cancer: a series of 18 cases. Psychosomatics 2016;57(1):71–81

5 Scalzo SJ, Bowden SC, Ambrose ML, Whelan G, Cook MJ. Wernicke-Korsakoff syndrome not related to alcohol use: a systematic review. J Neurol Neurosurg Psychiatry 2015;86(12): 1362–1368

6 Trueg A, Borho T, Srivastava S, Kiel P. Thiamine deficiency following umbilical cord blood transplant. Nutr Clin Pract 2013;28(2): 223–225

7 Friedenberg AS, Brandoff DE, Schiffman FJ. Type B lactic acidosis as a severe metabolic complication in lymphoma and leukemia: a case series from a single institution and literature review. Medicine (Baltimore) 2007;86(4):225–232

8 Renthal W, Marin-Valencia I, Evans PA. Thiamine deficiency secondary to anorexia nervosa: an uncommon cause of peripheral neuropathy and Wernicke encephalopathy in adolescence. Pediatr Neurol 2014;51(1):100–103

9 Manzanares W, Hardy G. Thiamine supplementation in the critically ill. Curr Opin Clin Nutr Metab Care 2011;14(6): 610–617

10 Lima LF, Leite HP, Taddei JA. Low blood thiamine concentrations in children upon admission to the intensive care unit: risk factors and prognostic significance. Am J Clin Nutr 2011;93(1):57–61

11 Costa NA, Gut AL, de Souza Dorna M, et al. Serum thiamine concentration and oxidative stress as predictors of mortality in patients with septic shock. J Crit Care 2014;29(2):249–252

12 Seear M, Lockitch G, Jacobson B, Quigley G, MacNab A. Thiamine, riboflavin, and pyridoxine deficiencies in a population of critically ill children. J Pediatr 1992;121(4):533–538

13 Maiorana A, Vergine G, Coletti V, et al. Acute thiamine deficiency and refeeding syndrome: Similar findings but different pathogenesis. Nutrition 2014;30(7–8):948–952